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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
(SAN JOSE DIVISION)

GILEAD SCIENCES, INC., Plaintiff, v. MERCK & CO., INC., MERCK SHARP & DOHME CORP. and ISIS PHARMACEUTICALS, INC., Defendants.	Case No. 5:13-cv-04057-BLF/PSG **GILEAD SCIENCE, INC.'S RESPONSIVE CLAIM CONSTRUCTION BRIEF** Date: April 3, 2015 Time: 9:00 a.m.

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I. INTRODUCTION

Plaintiff Gilead Sciences, Inc. respectfully requests that the Court adopt its proposed constructions for the disputed claim terms "administering" and "compound."

Just shy of a year ago, Gilead received approval from FDA to market and sell its revolutionary treatment for HCV, Sovaldi®, which contains the active ingredient sofosbuvir. Sofosbuvir will change the lives of millions of people worldwide who are infected with the deadly hepatitis C virus. Before sofosbuvir, the standard course of treatment made patients so ill that many preferred the disease to the therapy. Today those same patients can take a simplified treatment regimen with far fewer side effects and be cured in a matter of months.

One of the key aspects of sofosbuvir's design is the placement of a fluorine atom (F) oriented down, and a methyl group (CH_3) oriented up, at a particular place (the 2' position) on the sugar ring of the molecule. A second is sofosbuvir's design as a particular prodrug—it is inactive until transformed by enzymes in the body to an active form. Not just any prodrug design will work; sofosbuvir uses a chemical structure called a "phosphoramidate" to ensure that the correct active molecule is delivered to liver cells to stop replication of the HCV virus. Inside the cell, that phosphoramidate structure ultimately converts to a triple phosphate structure that, combined with the 2' fluoro/methyl design and other aspects of Gilead's innovation, leads to the suppression of the virus and a cure for the patient.

When it became clear that this 2' fluoro/methyl and phosphoramidate design as embodied in sofosbuvir would forever alter the landscape of HCV treatment, Merck came knocking on Gilead's door with its two patents in hand. Merck demanded an astounding 10% royalty on future sales of sofosbuvir. (Doc. 1-3.) Merck demanded that royalty despite knowing that it sells no product covered by those patents, and that neither it nor its collaborator Isis played any role in the series of innovations that resulted in sofosbuvir—a point exemplified by the fact that not even one of the more than one hundred compounds described in the patents has either the 2' fluoro/methyl or phosphoramidate design of sofosbuvir. Unwilling to agree to this outrageous

demand, Gilead filed suit seeking a declaratory judgment that Defendants' patents are invalid and not infringed.

Defendants' '499 and '712 patents teach a class of drug molecules that can be synthesized and provided to patients to treat HCV, either as themselves or in the form of certain identified prodrugs. Gilead asks this court to construe the asserted claims consistent with those teachings and true to the scope of Defendants' alleged inventions.

The asserted claims either directly claim compounds or the administration of compounds to treat HCV. As used in the intrinsic record, the disputed claim term "compound" refers to synthetically produced compounds only. The claims and written description ***never***—in words or figures—describe compounds produced in the body. In stark contrast, the patents include columns of text describing how compounds and their pharmaceutically acceptable salts or specific prodrug forms can be made in the lab, and how those synthetic compounds may be combined with other drugs at the time they are given to patients for therapy. The patents lack any description about how the body may transform any of the described compounds or prodrugs, or what form those transformed compounds or prodrugs would take, let alone describe that the claimed "compounds" are generated inside the body.

Similarly, the intrinsic record shows that the activity encompassed by the claim term "administering" is simply "providing" a synthetic compound or prodrug to an individual in need without reference to how the body may transform it, consistent with Gilead's proposed construction. Nothing in the '499 patent changes the ordinary meaning of "administering" to encompass in vivo transformations. And while the '499 patent refers to administering prodrugs of the invention, that does not mean that any kind of prodrug falls within the claims. Rather, the patentees described a limited set of prodrugs in the written description, sought to expressly claim only a narrower group of that specific set of prodrugs, and ultimately bargained with the Patent Office to secure claims covering just that. There is no mention in the patent of sofosbuvir's phosphoramidate design that Defendants' infringement-driven construction seeks to cover.

The intrinsic record here supports Gilead's constructions of "compound" and "administering" and the Court should reject Defendants' efforts to expand those constructions to capture a drug whose innovations are not to be found in the properly construed patent claims.

II. RELEVANT TECHNOLOGY

A. Hepatitis C

Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV), which primarily targets the liver. ('499 patent at 1:29-33.)[1] Left untreated, HCV ultimately leads to liver disease and is the primary cause of liver cancer. (*Id.* at 1:29-33, 1:40-42.) HCV is a silent disease. Infected individuals can go years, or even decades, without experiencing symptoms until liver damage becomes apparent. In the United States over 4 million people carry the virus, and of them, the majority develop chronic infection, which in recent years has caused more deaths than HIV/AIDS. (*See id.* at 1:33-40.)

Because of the incredibly rapid rate at which the virus replicates in the body, as well as the large number of mutations that take place as the virus replicates, developing an effective HCV therapy has been challenging. (*See id.* at 2:4-31.) Traditionally, chronic HCV infection has been treated with a combination of antiviral medicines that must be taken for prolonged periods—up to 48 weeks—and are regularly associated with debilitating side effects. (*See id.* at 1:45-48.) Because of the treatment timeline and side effects, patients frequently discontinue treatment. The need for more effective and tolerable HCV treatments prompted many companies to search for effective alternative treatments. (*Id.* at 1:45-2:31.)

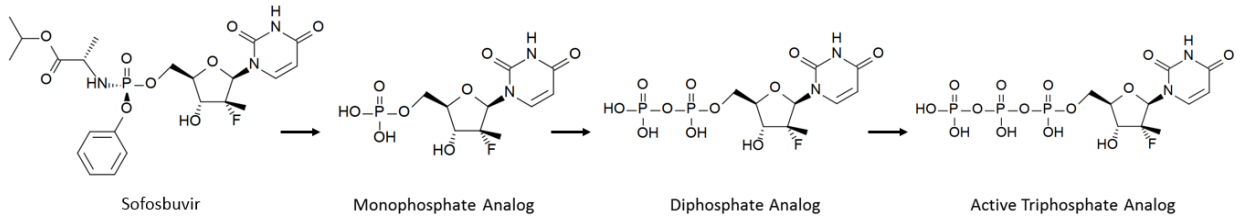
B. Sofosbuvir: Gilead's Groundbreaking HCV Treatment

Sofosbuvir represents a seismic change in HCV therapy. It shortens HCV treatment duration to as little as 12 to 16 weeks, providing the millions of people suffering from HCV with a far more effective and less burdensome treatment than any other currently available. When used in combination with other antiviral agents, sofosbuvir effectively eliminates the virus,

[1] All citations herein to the '499 patent refer to Docket No. 91-2 (Rabinowitz Declaration Exhibit 1).

achieving cure rates of up to 93%. It is no wonder, then, that the FDA's December 2013 approval of sofosbuvir was hailed throughout the scientific and popular press as a major breakthrough in HCV treatment. (Flanagan Decl., Ex. A, Wall Street Journal, Dec. 6, 2013.)

Chemically speaking, sofosbuvir is a nucleotide prodrug—specifically, a phosphoramidate prodrug—of a nucleotide analog. As a prodrug, sofosbuvir is not active against HCV in and of itself. Rather, the body must transform, or metabolize, sofosbuvir into another chemical form—a triphosphate—that is active against HCV. (*See* Flanagan Decl., Ex. B, Sovaldi™ Prescribing Information, at § 12.4.) The following diagram illustrates some of the steps the body takes to transform sofosbuvir into the active triphosphate analog[2]:



While the triphosphate analog of sofosbuvir could be provided to the patient, Gilead learned that, due to various biological hurdles, it rapidly deactivates and cannot efficiently treat the virus when ingested in that form. (*See* Flanagan Decl., Ex. C, Sofia et al., at 7203).) Only by delivering a precursor of the triphosphate analog to the body as a prodrug can the triphosphate analog be created and efficiently treat the disease. (*See id.*)

C. Defendants' '499 and '712 Patents Claim Large Classes of Nucleosides Alleged to Treat HCV

Defendants Merck and Isis obtained the two patents-in-suit as part of their investigations of nucleoside derivatives that inhibit viral replication as potential HCV treatments, although those investigations never resulted in a promising cure for HCV, and the patents cover no drug sold by either Defendant. The '499 patent includes two claims, both of which relate to methods

[2] Sofosbuvir undergoes a series of complex transformations in vivo to ultimately treat HCV, only some of which are depicted in this illustration. Gilead will illustrate and explain the in vivo transformations of sofosbuvir in detail during the Technology Tutorial.

of treating HCV infection by administering an effective amount of a large class of compounds having a generic structural formula, either alone or in combination with another HCV treatment. The '712 patent includes eleven claims, each of which directly claims classes of compounds with various generic structural formulas.

III. LEGAL STANDARDS FOR CLAIM CONSTRUCTION

Claim construction begins with the intrinsic evidence—namely, the specification, including the claims and written description, and the prosecution history. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-17 (Fed. Cir. 2005) (en banc). These are "the most significant" sources for determining the meaning of claim terms. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

Claim terms "'are generally given their ordinary and customary meaning'" as understood by a person of ordinary skill in the art at the time of the invention. *Phillips*, 415 F.3d at 1312 (quoting *Vitronics*, 90 F.3d at 1582). The ordinary and customary meaning of a claim term is determined with reference to the specification, "because 'the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent.'" *AquaTex Indus., Inc. v. Techniche Solutions*, 419 F.3d 1374, 1380 (Fed. Cir. 2005) (quoting *Phillips*, 415 F.3d at 1313). The specification is "'the single best guide to the meaning of a disputed term,'" and is usually dispositive. *Phillips*, 415 F.3d at 1315 (quoting *Vitronics*, 90 F.3d at 1582). Indeed, it is "entirely appropriate for a court, when conducting claim construction, to rely heavily on the written description for guidance as to the meaning of the claims." *Id.* at 1317.

The prosecution history should also be consulted because it "inform[s] the meaning of the claim language by demonstrating how the inventor understood the invention." *Id.* In addition, it "protects the public's reliance on definitive statements made during prosecution." *Omega Eng'g, Inc., v. Raytek Corp.*, 334 F.3d 1314, 1324 (Fed. Cir. 2003).

There are two exceptions to the foregoing "general rule" of claim construction: "1) when a patentee sets out a definition and acts as his own lexicographer, or 2) when the patentee

disavows the full scope of a claim term either in the specification or during prosecution." *Thorner v. Sony Computer Entm't Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012). When the specification reveals that the patentee has set out a special definition for a claim term, "the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316. When the patentee has "unequivocally disavowed a certain meaning to obtain his patent, the doctrine of prosecution disclaimer attaches and narrows the ordinary meaning of the claim congruent with the scope of the surrender." *Omega*, 334 F.3d at 1324.

Courts may also consider extrinsic evidence, such as dictionaries and treatises, to "help educate the court regarding the field of the invention and . . . help the court determine what a person of ordinary skill in the art would understand claim terms to mean," but such evidence should be considered in the context of the intrinsic record. *Phillips*, 415 F.3d at 1319. Extrinsic evidence cannot be used to "vary or contradict the claim language. Nor may it contradict the import of other parts of the specification." *Vitronics*, 90 F.3d at 1584.

The claim construction "that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998).

IV. ARGUMENT

A. "Compound" ('499 patent, claims 1, 2; '712 patent, claims 1-3, 5, 7, 9-11)

Gilead's Proposed Construction	Defendants' Proposed Construction
The term "compound" refers to synthetically produced compounds only.	a substance that consists of two or more chemical elements in union.

The parties' dispute over the meaning of the claim term "compound" is whether it encompasses synthetically produced compounds only, as Gilead proposes, or further extends to compounds transformed by the body after ingestion—*i.e.*, metabolites that include the mono, di, and triphosphate analogs of sofosbuvir—as Defendants urge. This dispute goes to the heart of Defendants' infringement proofs. Under Gilead's construction and the correct view of the

claims, the accused compound sofosbuvir cannot infringe any asserted claim of the '712 patent because it is a phosphoramidate prodrug, and not a mono, di, or triphosphate analog as required by those claims. Only after the body transforms sofosbuvir into its mono, di, or triphosphate analogs could those resulting metabolites infringe the claims. Thus, the only way that Defendants can prove infringement of the asserted compound claims is to expand their scope to encompass sofosbuvir's metabolites, which are not synthetic, but instead created in the body, and treat them as claimed "compounds." But this is inconsistent with the patents' description of the invention. As demonstrated below, the patents-in-suit only contemplate synthetically generated compounds, and Gilead's proposed construction should be adopted for that reason.

Ignoring the intrinsic evidence, Defendants choose to support their proposed construction with reference to only one of the nearly 300 uses of the term compound in the written description, three dictionary definitions, and *Markman* rulings in different cases involving different patents. Defendants' approach is wrong because it asks this court to construe the term "compound" in a vacuum and without reference to the intrinsic evidence which, as demonstrated below, compels adoption of Gilead's construction. *Taurus IP, LLC v. DaimlerChrysler Corp.*, 726 F.3d 1306, 1320 (Fed. Cir. 2013) ("The [claim term] cannot be construed in a vacuum . . . . Instead, it must be construed in light of the written description in which it resides.").

1. The Claim Language Supports Construing "Compound" With Reference to Synthetic Compounds Only

The plain language of the claims is consistent with Gilead's construction that "compound" refers to synthetically produced compounds only. All of the asserted claims recite a compound of a specific formula or a "pharmaceutically acceptable salt" thereof. The patents describe pharmaceutically acceptable salts as "salts ***prepared*** from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids." ('499 patent at 37:33-37; '712 patent at 143:2-146:61 (emphasis added).)[3] Thus, the claims'

[3] All citations herein to the '712 patent refer to Docket No. 91-4 (Rabinowitz Declaration Exhibit 3).

reference to "pharmaceutically acceptable salts" of the claimed compounds, which are synthetically prepared—not generated by the body—is consistent with Gilead's proposed construction. Indeed, the specification states that "[t]he compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt," further referring to the untransformed form of the compounds. ('499 patent at 37:32-33.) *See Marion Merrell Dow Inc. v. Baker Norton Pharms., Inc.*, 948 F. Supp. 1050, 1054 (S.D. Fla. 1996) (relying in part on the claims' recitation of "pharmaceutically acceptable salts" to construe "compound" with respect to synthetic compounds only); *see also In re Omeprazole Patent Litig.*, No. MDL 1291, 2001 WL 585534, at *4-5 (S.D.N.Y. May 31, 2001) (relying in part on the claims' recitation of "pharmaceutically acceptable anions" to construe "compound" with respect to synthetic compounds only).

Claim 2 of the '499 patent includes additional language showing that the claims refer only to synthetically produced compounds. Claim 2 provides that the compound of claim 1 is administered ***in combination with*** another agent active against HCV infection selected from a group of several options. ('499 patent at 138:17-25.) The parties have agreed that "in combination with" means "'together with,' whether given separately at different times during the course of therapy or concurrently in divided or single combination forms." (Doc. 86 at 2.) The "in combination with" claim language references synthetic compounds only, since it relates to how and when the compounds are given to patients, and ***not*** how the body transforms those compounds.

From the foregoing claim language, skilled artisans would understand that the claims cover synthetically prepared compounds, and do not extend to compounds that are generated within the body.

2. The Written Description Solely Describes Synthesizing the Claimed Compounds, Not Generating Them In Vivo

The written description demonstrates that the inventors communicated to the public that their alleged invention encompasses synthetic compounds and no more. That much is plain from

the entirety of the patents' written description, which refers to "novel" compounds having various structural formulae. (*See, e.g.*, '499 patent at 5:63-66; 7:65-8:2; 20:36-39; 25:38-42.)[4] The disclosed "novel" compounds are non-natural, man-made compounds that have been engineered by the inventors to supposedly interfere with viral replication. (*Id.* at 2:31-39.)

Importantly, the written description ***never*** refers to compounds or metabolites generated in vivo by the body. *Marion Merrell Dow*, 948 F. Supp. at 1055 (excluding metabolically produced compounds from the scope of the claim term "compound" in part because "the specification contains no reference whatsoever to [a compound] created inter vivo by metabolism"). To the contrary, the patents solely focus on preparation of "novel" compounds by synthetic methods. Indeed, the patents include a section entitled "Preparation of the Nucleoside Compounds and Derivatives of the Invention" that spans nearly 100 columns and solely refers to synthetically produced compounds. (*See, e.g.*, '499 patent at 38:20-40:42; *id.* at cols. 40-131.) This section describes preparing the compounds "following synthetic methodologies well-established in the practice of nucleoside and nucleotide chemistry." (*Id.* at 38:23-31.) It includes a general synthetic "scheme" for "preparation of the compounds of the present invention." (*Id.* at 38:32-37.) It also includes specific instructions and/or references to published synthetic methods for preparing each of the over 150 exemplary compounds that are not commercially available. (*Id.* at 40:45-131:67.)

Throughout this section, the written description refers to "compounds" being prepared according to the disclosed methods, all of which take place on a lab bench, and not within the body. (*See, e.g.*, *id.* at 40:66-67 (Example 1); 41:20-21; 42:38-67 (Example 6); 43:56-44:35 (Example 9); etc.; *see also id*. at 37:1-10 (describing laboratory techniques to separate compounds).) And this section clearly states that "***final compounds***" of the invention are prepared by synthetic techniques:

[4] As Defendants agree that the '499 and '712 patents "share a largely identical specification," (Doc. 91 at 1), Gilead provides citations only to the '499 patent's written description in the interest of brevity.

> The examples below provide citations to literature publications, ***which contain details for the preparation of final compounds of the present invention. The nucleoside compounds of the present invention were prepared according to the procedures detailed in the following examples***. . . . Those skilled in the art of nucleoside and nucleotide synthesis will readily appreciate that ***known variations of the conditions and processes of the following preparative procedures can be used to prepare these and other compounds of the present invention***.

(*Id.* at 40:28-41 (emphases added).) Thus, the only description in the patents of producing the claimed, or "final" compounds is preparation by synthetic means. By contrast, the specification nowhere refers to any claimed compounds being created by in vivo metabolism.

Aside from methods to synthesize various compounds, the written description contains other passages that demonstrate the claim term "compound" extends only to synthetically prepared compounds. For example, the written description repeatedly refers to "pharmaceutical compositions" containing the described nucleoside compounds. (*See, e.g.*, *id.* at 9:17-20; 33:35-45.) It also states that an "aspect of the present invention provides for the use of nucleoside compounds and derivatives thereof and their pharmaceutical compositions for the manufacture of a medicament" to treat HCV. (*Id.* at 34:13-25.) It also describes "combining any of the compounds described above and a pharmaceutically acceptable carrier," which "must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof." (*Id.* at 33:39-41; 33:31-34.) The pharmaceutical compositions "encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier." (*Id.* at 32:1-4.) From these descriptions, it is clear that the inventors contemplated that the claimed compounds could and would be included within pharmaceutical compositions. In order to do so, the compounds must be synthetic—metabolites generated in the body could not be included within a pharmaceutical composition prepared by man.

The written description—like the claims—refers to pharmaceutically acceptable salts of the "inventive" compounds and their administration in that form. (*See id.* at 37:32-38:9.) As discussed above, the specification describes preparing pharmaceutically acceptable salts of the claimed compounds with reference to inorganic and organic acids and bases, not by in vivo

conversion in the body. (*Id.* at 37:33-37.) These pharmaceutically acceptable salts do no occur via in vivo transformation. And many of the "pharmaceutically acceptable salts" referenced in the patents do not occur naturally—*e.g.*, methylbromide, methylnitrate, tosylate, N-N-dibenzylethylenediamine, and N-ethylmorpholine. (*Id.*) *See In re Omeprazole*, 2001 WL 585534 at *5 (relying in part on references to pharmaceutically acceptable salts that do not occur in vivo to construe "compound" with reference to synthetic compounds only). Moreover, the written description refers to combinations of the compounds of the present invention and other HCV agents, again without reference to any in vivo transformations of those compounds. ('499 patent at 32:9-33:30.) These descriptions of the "invention" further support Gilead's proposed construction.

The written description also includes long lists of "novel compounds," including their pharmaceutically acceptable salts and corresponding 5' triphosphates. (*Id.* at 15:29-20:35; 25:11-37; 27:29-29:54.) But not once does the patent state that those salts or corresponding triphosphates are produced other than by synthetic means, let alone by conversion in the body. In fact, the patents include instructions for synthesizing pharmaceutically acceptable salts and triphosphates (Examples 86-87), and also steps for preparing a specific compound (Example 62) and its corresponding triphosphate (Example 129). (*Compare* '499 patent at 71:48-75:20 (Example 62), *with id.* at 88:63-89:39 (Examples 86-87), 110:10-42 (Example 129).) And the patents expressly contemplate ***synthetic*** mono, di and triphosphate compounds, which are encompassed by the disclosed structural formulas,[5] "as the active ingredient in intimate admixture with a pharmaceutical carrier." (*See id.* at 34:40-43; *see also id.* at 34:26-30.) Thus, the written description describes including synthetic mono, di, and triphosphate derivatives directly into a formulation to be administered to a patient. Although those forms could be produced by the body's metabolism, the written description teaches synthesizing them so they can be directly ingested by the patient.

[5] As will be explained in Gilead's technology tutorial, the "Y" group in the structural formulas can be a triphosphate ($P_3O_9H_4$), diphosphate ($P_2O_6H_3$), or monophosphate ($P(O)R^9R^{10}$, where R^9 and R^{10} are hydroxyl).

In short, the totality of the written description—which is usually dispositive in claim construction—plainly signals that the claims encompass only synthetically produced compounds. *See Phillips*, 415 F.3d at 1315. Remarkably, Defendants did not acknowledge—let alone address—any of these passages in their opening brief.

3. Defendants' Proposed Construction Ignores the Intrinsic Record

Defendants' proposed construction of "compound" is wrong because it does not take into account the plain language of the claims and the clear import of the written description, places too much weight on dictionary definitions, and relies on constructions adopted by other courts considering different patents with different claim language, different specifications, and different file histories. Defendants' technical meaning of "compound" is divorced from the context of the specification. *Schriber–Schroth Co. v. Cleveland Trust Co.*, 311 U.S. 211, 217 (1940) ("The claims of a patent are always to be read or interpreted in light of its specifications."); *Thorner*, 669 F.3d at 1365 ("The words of a claim are generally given their ordinary and customary meaning as understood by a person of ordinary skill in the art when read in the context of the specification and prosecution history.").

As demonstrated above, the claims and written description communicate to the skilled artisan that the claimed compounds are synthetically produced. Defendants recite only one phrase in the patents-in-suit to suggest the term "compound" extends to compounds produced in the body: the patents' alleged definitions of "administration of" and "administering a." (Doc. 91 at 10.) Defendants suggest that because those terms refer to providing a ***prodrug*** of a compound of the invention, the term "compound" encompasses compounds "produced in the body by metabolism of a prodrug that is given to a patient." (*Id.*) Defendants read too much into this reference to a prodrug. As demonstrated below, the patent's description of "administering a" does not take into account anything that happens to a compound once it is in the body. The description only clarifies the scope of what can be administered—specified compounds or prodrugs of such compounds that are described in the patents-in-suit. Moreover, the written description uses the term "prodrug" in only two other instances, both of which refer to prodrugs

in the synthetic sense and without reference to products of their metabolism in the body. ('499 patent at 38:11-19 (describing pharmaceutically acceptable esters as acceptable prodrugs); 77:57-78:30 (Example 72) (chemical synthesis of SATE prodrug moiety)).

Lacking sufficient support in the specification, Defendants turn to dictionary definitions to back their construction. But "heavy reliance on the dictionary divorced from the intrinsic evidence risks transforming the meaning of the claim term to the artisan into the meaning of the term in the abstract." *Phillips*, 415 F.3d at 1321. That is precisely what Defendants' "technical dictionaries" do. (Doc. 91 at 11.) *See also Free Motion Fitness, Inc. v. Cybex Int'l, Inc.*, 423 F.3d 1343, 1348 (Fed. Cir. 2005) ("The court must ensure that any reliance on dictionaries accords with the intrinsic evidence . . . .").

Defendants' cited case law does not compel adoption of their proposed construction. As an initial matter, Defendants make no attempt to demonstrate that their two cited cases, *Aventis* and *Ortho-McNeil*, deal with "comparable patents," let alone instructive intrinsic records. (Doc. No. 91 at 11.) Even if they did, another district court's construction of the same term in a different patent is not binding on this court. *See Shuffle Master, Inc. v. MP Games, LLC*, No. 3:04-CV-0407-ECR-RAM, 2005 WL 6220114, at *17 (D. Nev. Dec. 20, 2005) ("[W]hile how other courts have interpreted the [same language] is instructive, it is not binding given the case-by-case nature of claim construction and the requirement that the ordinary meaning of a word also match the claim meaning."). Moreover, those cases do not present the same dispute as here. Unlike here, the parties in *Aventis* did not "particularly contest[]" the construction of "compound." *Aventis Pharma Deutschland GmbH v. Lupin Ltd.*, No. 2:05cv421, 2006 WL 1314413, at *5 (E.D. Va. May 11, 2006). In *Ortho-McNeil*, the parties disputed whether "compound" could encompass a single molecule or only a "sizeable quantity" of molecules, not whether "compound" reaches beyond synthetically produced compounds. *Ortho-McNeil Pharm. Inc. v. Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 727 (N.D.W. Va. 2004). And in *Ortho-McNeil*, the district court placed heightened emphasis on dictionary definitions in arriving at its construction, a practice the Federal Circuit has since rejected. *Id.* at 722, 728 (citing *Texas*

Digital Sys. v. Telegenix, Inc., 308 F.3d. 1193, 1202-04 (Fed. Cir. 2002)); *see Phillips*, 415 F.3d at 1319-23 (discussing the problems with *Texas Digital* line of cases and over-reliance on dictionary definitions in claim construction).

In brief, Gilead's proposed construction of "compound" is consistent with the intrinsic evidence whereas Defendants' proposed construction of "compound" wrongly ignores it in favor of extrinsic evidence.

B. **"Administering" ('499 patent, claim 1)**

Gilead's Proposed Construction	Defendants' Proposed Construction
providing a compound of the invention or a prodrug of a compound of the invention to the individual in need without reference to in vivo transformations of those compounds or prodrugs. The phrase "prodrug of a compound" means those prodrugs that are expressly claimed.	providing a compound of the invention or a prodrug of a compound of the invention to the individual in need.

1. The Claim Term "Administering" Does Not Encompass In Vivo Transformations Of the Claimed Compounds or Prodrugs

Gilead's proposed construction of "administering"—which builds off of the '499 patent's description that "'administering a' should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need"—is consistent with that term's ordinary meaning, including as used in the claims and written description. ('499 patent at 32:5-8.) Nothing in the intrinsic record suggests that the patentees altered the ordinary meaning of "administering" to refer to in vivo compound transformations. Gilead's proposed construction merely clarifies that point. And such clarification is necessary now because Defendants' infringement theory for the '499 patent relies on the fact that the body transforms sofosbuvir—which is not expressly covered by the claims—into other compounds that are expressly claimed.

a. Gilead's Construction Is Consistent with the Ordinary Meaning of "Administering"

In the context of pharmaceuticals and health care, "administering" has a readily understood meaning. Health professionals administer treatments to patients in many different ways—for example, by tablet or capsule, injection, or eye drop. Patients can self-administer many type of treatments. Indeed, people regularly administer ibuprofen or aspirin to themselves. These acts of "administering" describe nothing more than getting a treatment into the patient's body. In other words, administration is complete at the point when the patient swallows a tablet, a syringe is removed from the injection site, or an eye drop is applied to the eye. Administering does not extend beyond those acts to encompass whether and how the body transforms a drug after it gets in the body. This commonsense view of "administering" is just how that term is described in the dictionary. Administer is defined as "to apply as a remedy: *administer a sedative*" and "to mete out; dispense." (Flanagan Decl., Ex. D, American Heritage Dictionary, at GILEAD988.) It is not defined to follow a drug's journey through the body.

b. The Plain Language of the Claims Does Not Refer To In Vivo Transformations

The claims confirm that the ordinary meaning of "administering" does not include how the body transforms the compounds or prodrugs that are provided to those in need. There is no language in the claims that instructs a skilled artisan to take into account in vivo transformations of the compounds provided to patients, and Defendants do not point to any. To the contrary, the claims include language that is consistent with a timeframe before any in vivo transformations take place.

First, claim 1 refers to "pharmaceutically acceptable salt[s] or acyl derivatives" of the recited compounds. ('499 patent at 137:4-6.) As described above, those forms of compounds and prodrugs are prepared in the lab, not by the body. (*Id.* at 37:32-37 (describing how to make pharmaceutically acceptable salts); 38:11-19 (describing pharmaceutically acceptable acyl derivatives).) Second, claim 2 refers to administering the claimed compounds or their pharmaceutically acceptable salts and acyl derivatives "in combination with" other active agents.

The parties' agreed construction of "in combination with" describes when and in what form (together or separately) the two drugs are given to a patient. (Doc. 86 at 2.) That agreed construction does not take into account any in vivo transformations of those compounds. Taken as a whole, the claim language is consistent with giving compounds to individuals and inconsistent with tracking how the body may transform those compounds.

c. The Written Description Is Consistent with Gilead's Proposed Construction of "Administering"

i. The Patent Equates "Administering" With "Providing"

The '499 patent states that "'administering a' compound should be understood to mean ***providing*** a compound of the invention or a prodrug of a compound of the invention to an individual in need." ('499 patent at 32:5-8 (emphasis added).) The patent uses the verb "providing" to describe how a patient receives a compound or prodrug according to the claimed method. (*Id.*) The ordinary meaning of "provide" is give to, supply, or make available. (Flanagan Decl. Ex. D, American Heritage Dictionary, at GILEAD989 (defining "provide"); *id.* Ex. E, Webster's Ninth New Collegiate Dictionary, at GILEAD995 (same).). In the context of the claims, then, "administering" means providing, supplying, giving, or making available a compound of the invention or a prodrug of a compound of the invention to an individual in need. In other words, providing stops when the patient receives the compound. As such, the ordinary meanings of both "administering" and "providing" do not take into account how the body processes the compound that is given to the patient, which is consistent with Gilead's proposed construction.

ii. The Patent Uses the Term "Administering" Consistent With Its Ordinary Meaning

Besides stating that "'administering a' . . . means . . .," the patent includes additional guidance on the meaning of "administering." In discussing combination therapy, the patent continues, "[t]he instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment, ***and the term 'administering' is to be interpreted***

accordingly." (*Id.* at 32:36-39 (emphasis added).) As described above with respect to the claim language, the patent puts the action of "administering" in the same time frame as combination therapy, which relates to when and in what dosage form(s) different drugs are given to patients, and not to what happens to those drugs once in the body. The claim term "administering" should be read in conjunction with this language, and that is what Gilead's proposed construction does.

Other portions of the written description confirm Gilead's proposed construction. For example, the patent sates that "[t]he compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt." (*Id.* at 37:32-33.) As described above, pharmaceutically acceptable salts are prepared by man, thus putting "administering" in a timeframe before the body transforms the compounds given to a patient.

The patent also describes various dosage forms that can be administered and routes for administering the compounds, both of which are consistent with the same timeframe. (*See id.* at 34:31-37, 35:39-43 (describing various acceptable routes of administering the inventive compounds); *id.* at 34:58-35:38, 35:43-45 (describing various dosage forms suitable for the various routes of administration).) In describing these routes of administration and dosage forms the patent never refers to in vivo transformation of the claimed compounds. The court should decline to read more into the action of "administering" than is warranted by the patent's description. *See Hoffman La-Roche Inc. v. Apotex Inc.*, No. 07-4417, 2010 WL 1875569, at *10 (D.N.J. May 10, 2010) (construing "'administering' to end at the point at which the body has received the medication and begins to transform it from its initial form" based on the intrinsic record); *Schering Corp. v. Glenmark Pharms. Inc.*, No. 07-1334, 2008 WL 4307189, at *8 (D.N.J. Sept. 16, 2008) (construing "administering" to exclude metabolites formed in vivo upon administration based on the intrinsic and extrinsic record).

Defendants wrongly imply that their proposed construction is correct because it captures the patent's express definition of "administering." As described above, the patent does not only use the language in Defendants' construction to describe "administering." It includes other language by which "administering" is to be "interpreted accordingly" that Defendants ignore.

('499 patent at 32:36-39.) A patent's alleged definition of a claim term is not necessarily the correct construction; the entire intrinsic record must be reviewed to arrive at the correct construction. *Allergan, Inc. v. Apotex, Inc.*, 754 F.3d 952, 957-58 (Fed. Cir. 2014) (approving district court's construction that "read[] the patentee's own lexicography in light of the whole specification"); *Trading Techs. Int'l, Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1353 (Fed. Cir. 2010) ("The district court's definition may seem narrower than the inventors' express definition at first glance. However, the claims, the rest of the specification, and the prosecution history support the district court's definition.").

Defendants also fail to explain why the patent's description of "administering," which includes providing prodrugs of the inventive compounds to persons in need, should mean that the act of "administering" includes not only compounds given to the patient, but also the active compound that ultimately is created in the liver, and also other compounds generated by the body in intermediate metabolic steps. (Doc. 91 at 8-9.) Defendants offer nothing beyond attorney argument to substantiate that view. The description itself does not refer to in vivo transformations. It merely refers to providing a specific synthetic form of the compound—a prodrug—to an individual. It does not indicate that "administering" or "providing" encompasses any action beyond those terms' ordinary meaning which, as described above, is synonymous with giving and supplying. Thus, it is Defendants, not Gilead, that are adding to the claims an "extraneous limitation[] having nothing to do with the proper meaning of 'administering'" by permitting "administering" to reach beyond the simple act of providing a compound to an individual in need. (Doc. 91 at 7.)

iii. Extrinsic Evidence Supports Gilead's Construction

Defendant Merck's own seminal technical publication—the Merck Manual—demonstrates that skilled artisans draw a clear line between compound administration and metabolite formation in vivo. The Merck Manual defines "pharmacokinetics" as the "[s]tudy of the time course of a drug and its metabolites in the body after administration by any route." (Flanagan Decl. Ex. F, The Merck Manual of Diagnosis and Therapy, at GILEAD1002.) As

explained by another court, that "definition makes clear that metabolites form only *after* a drug is 'administered.'" *Glenmark*, 2008 WL 4307189, at *8. The Merck Manual also includes a section on "Drug Input and Disposition" that describes drug absorption, bioavailability, distribution and elimination. (Flanagan Decl. Ex. F, The Merck Manual of Diagnosis and Therapy, at GILEAD999-1002.) This section distinguishes administration from the other steps in a drug's journey through the body. Indeed, it defines absorption as the "process of drug movement *from the administration site* to the systemic circulation." (*Id.* at GILEAD999 (emphasis added).)

In addition to Merck's own technical dictionary, other dictionary definitions support Gilead's proposed construction, which draws a line between administration and how a compound is transformed in the body. As described above, the patent uses the verb "providing" to describe the action of administering, and the definition of "provide" is "to furnish; supply" and "to make available." (Flanagan Dec., Ex. D, American Heritage Dictionary, at GILEAD989; *id.* E*x.* E, Webster's Ninth New Collegiate Dictionary, at GILEAD995.) Dictionary definitions for "administer" are consistent, defining "administer" as "to apply as a remedy;" and "to mete out; dispense." (Flanagan Dec. Ex. D, American Heritage Dictionary, at GILEAD988.) None of these definitions for "provide" or "administer" suggest that those actions extend beyond giving a compound to a patient, which is consistent with the intrinsic record's treatment of "administering" and Gilead's proposed construction.

iv. Defendants' Case Law Does Not Compel Adopting Defendants' Construction Over Gilead's

Defendants cite various cases to support their reading that "administering" includes in vivo transformations, but those cases either do not construe that claim term or are readily distinguishable. For example, *Zenith* does not address the construction of the claim terms "administering" or "compound," nor could it, because the asserted claims do not recite those terms. Rather, *Zenith* considered whether an accused product that converted in a patient's stomach into the patented compound infringed. *Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*,

19 F.3d 1418, 1420-22 (Fed. Cir. 1994). Although the *Zenith* court concluded that the claim in question was "not limited to the compound in its pre-ingestion form," *id.* at 1422, other courts have refused to apply the outcome of *Zenith* in construing the term "administering" because *Zenith*'s outcome was fact-specific and based on the relevant prosecution history. *See, e.g.*, *Glenmark*, 2008 WL 4307189, at *5 n.9. Defendants also cite *Schering Corp. v. Geneva Pharms. Inc.*, 339 F.3d 1373, 1381 (Fed. Cir. 2003), but like *Zenith*, *Schering* does not address the construction of the claim term "administering." Rather, *Schering* addresses compound claims, and there the parties ***agreed*** the asserted claims "cover[ed the claimed compound] in all its forms, including 'metabolized within the human body' and 'synthetically produced in a purified and isolated form.'" *Id.* at 1375-76.

Defendants' reliance on *Merck* is off base because that case did not address whether "administering" included in vivo transformations. There, the claim recited a method of using "4-amino-1-hydroxybutane-1,1-bisphosphonic acid" to treat a disease, and the accused product included a monosodium salt form of that drug, not the acid. *Merck & Co. v. Teva Pharms. USA, Inc.*, 347 F.3d 1367, 1369-70 (Fed. Cir. 2003). After reviewing the intrinsic record, the district court construed "4-amino-1-hydroxybutane-1,1-bisphosphonic acid" to include "both its free acid and sodium salt forms." *Merck & Co. v. TEVA Pharms. USA, Inc.*, 228 F. Supp. 2d 480, 486-89 (D. Del. 2002). The Federal Circuit affirmed that construction and the conclusion that "the claimed method of treatment by administration of the bisphosphonic acid is infringed whether administered as the pure acid form or in the form of the acid salt." *Merck*, 347 F.3d at 1372. Thus, *Merck* has no bearing on the present dispute.

Finally, Defendants again cite *Ortho-McNeil*, which relied on the dictionary definition of "administer" to conclude that a method claim reciting the step of "administering" a specific compound to a patient "does not contain a preingestion limitation." 348 F. Supp. 2d at 723, 730. The construction of "administering" adopted in *Ortho-McNeil* has since been criticized as overly-reliant on a dictionary definition of "administer," a definition that at least one court found

does not in any event include in vivo transformations. *Hoffman-La Roche*, 2010 WL 1875569, at *7-9.

2. "Administering" Encompasses Only Those Prodrugs That Are Claimed

The '499 patent does not alter the ordinary meaning of "administering," but instead uses that word to describe the scope of the compounds that may be administered. It does so by stating that "administering" includes "providing . . . a ***prodrug*** of the compound of the invention to the individual in need." ('499 patent at 32:5-8 (emphasis added).) Correctly viewed in light of the intrinsic record, "prodrug," and thus the claim term "administering," should be understood to encompass only those prodrugs that are expressly claimed. *See Advanced Fiber Techs. Trust v. J&L Fiber Servs., Inc.*, 674 F.3d 1365, 1373 (Fed. Cir. 2012) ("[I]n those cases in which the correct construction of a claim term necessitates a derivative construction of a non-claim term, a court may perform [a] derivative construction in order to elucidate the claim's meaning."). Defendants should not be allowed—through claim construction—to capture prodrugs that are neither described in the specification nor claimed.

i. The Intrinsic Record Shows That the Patentees Only Claimed A Limited Set of Prodrugs, Not Any Kind of Prodrug

The claims, written description and file history confirm Gilead's construction of "administering," which encompasses providing only the specific set of prodrugs that are claimed, and not any kind of prodrug, as Defendants' construction would permit.

The claims expressly recite only a limited group of prodrug moieties, including, for example, "acyl derivatives" and "SATE" prodrugs. ('499 patent at 137:2-6 ("a compound of structural formula III . . . or acyl derivatives thereof"); *id.* at 138:14-15 ("R^9 and R^{10} group are each independently . . . $OCH_2CH_2SC(=O)$t-butyl) . . . .).) The written description identifies "acyl derivatives" for use in "prodrug formulations." (*Id.* at 38:11-19.) And it depicts and describes the "SATE Prodrug Moiety." (*Id.* at 31:35-59; 77:57-67). By including only specific kinds of prodrugs in the claims, the claims give meaning to the term "prodrug" as used within the parties'

constructions of "administering" by expressly carving out from the universe of potential prodrugs only a specific and narrow subset of prodrugs.

The written description uses the term "prodrug" only three times, which together show that the concept of "prodrugs" in the context of the '499 patent is not all-encompassing. First, "prodrug" is used in describing the meaning of "administering." (*Id.* at 32:5-8). Second, the term is used in describing acyl derivatives as useful for preparing prodrugs. (*Id.* at 38:11-19.) Third, the term describes the "SATE" moiety. (*Id.* at 77:58). Beyond this, the written description does not define the concept of a "prodrug" or state that any kind of prodrug is suitable for use with the claimed compounds. Indeed, the written description does not indicate that any general category of "prodrugs" can be made from formula III, which is the formula referenced in claim 1. (*Id.* at 137:5.) Rather, the written description only includes a limited set of prodrug options within the description of formula III, including those that are expressly claimed, like the SATE group at R^9 and/or R^{10}. (*Id.* at 13:1-14:16.)

The file history supports Gilead's proposed construction because it both confirms that the patentees understood their invention to encompass only certain kinds of prodrugs and disclaims prodrugs that are not expressly covered by the claims. That disclaimer is evident from a review of claim 1 as originally presented and as amended during prosecution.

Issued claim 1 was presented as claim 53 during prosecution. (Flanagan Decl. Ex. G, '499 Patent File History Excerpts, at MERCK5809.) As initially presented, claim 1 expressly recited a certain group of "prodrugs" – ester prodrugs:

> Claim 53 (new) A method of treating hepatitis C virus (HCV infection) comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of structural formula III, or a pharmaceutically acceptable salt or ***ester prodrug*** thereof . . .

(*Id.* (emphasis added).) The remainder of the claim recited the additional specific prodrug forms that appear in issued claim 1, including the SATE group at R^9/R^{10}. (*See id.* at MERCK5810.) Despite using the term "administering," which the patent states includes providing "prodrugs" of a compound of the invention, the patentees chose to limit the scope of "prodrugs" claimed by

reciting only specific types of prodrugs in the claims. This initial claim language is consistent with the treatment of "prodrug" in the written description, and signals to the public that the patentees were only claiming those prodrugs expressly recited in the claim, and not *any* kind of prodrug. *Cf. Johnson & Johnston Associates, Inc. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002) ("[W]hen a patent drafter discloses but declines to claim subject matter, . . . this action dedicates that unclaimed subject matter to the public.").

By agreement with the Patent Examiner, the patentees amended the claim during prosecution to replace the phrase "ester prodrugs" with the phrase "acyl derivatives." (Flanagan Decl. Ex. G, '499 Patent File History Excerpts, at MERCK5818.) This revised claim language more closely tracks the written description, which describes esters and acyl derivatives as suitable for prodrug formulations but not once refers to "ester prodrugs." ('499 patent at 38:11-19.) Thus, consistent with the specification's treatment of "prodrug," the initial scope of the claims together with the claim amendment shows a clear disclaimer of any kind of prodrug in favor of just those that were both described and expressly claimed. *Omega*, 334 F.3d at 1323 ("[d]isclaimer . . . preclud[es] patentees from recapturing through claim interpretation specific meanings disclaimed during prosecution.").

If Defendants' construction controlled, the asserted '499 claims would cover any type of prodrug, which is inconsistent with the claims' express recitation of only certain types of prodrugs, the written description's limited treatment of prodrugs, and the claim scope Defendants expressly sought to obtain. Defendants struck a particular bargain with the Patent Office to secure allowance of claims that recite only certain prodrugs. Defendants should be held to that bargain now and not permitted to recapture through the construction of "administering" claim scope that the public never understood the claims to have.

ii. Defendants' Proposed Construction May Result in Invalidating the Asserted Claims of the '499 Patent

Defendants' claims should not be construed to cover the universe of all possible prodrugs because doing so would invalidate the '499 patent. Although Gilead maintains that the asserted

claims of the '499 patent are invalid for several reasons regardless of how the claims are construed, Defendant's proposed construction of "administering" would result in yet another reason why the claims are invalid. If "administering" had as broad a scope as Defendants' proposed construction would permit—*i.e.*, *any* kind of prodrug—then the '499 patent does not enable the full scope of the claims and they are invalid under 35 U.S.C. § 112. But under Gilead's construction, the claims encompass only those prodrugs that the written description describes and provides examples for, which would not pose the same problem.

Moreover, the '499 patent's claims would be invalid for indefiniteness if they encompassed any "prodrug," as Defendants' proposed construction permits. "[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014). Here, the patentees chose to use a structural formula defined with reference to numerous Markush groups to delineate the scope of the invention. Those Markush groups inform a skilled artisan, with reasonable certainty, about the claims' scope. But those Markush groups would be rendered meaningless if "prodrug" had no limits. For example, whereas the face of the claims only permit three types of R^9 and R^{10} groups ('499 patent at 138:14-15), Defendants' construction including any "prodrug" would render those R^9 and R^{10} groups virtually limitless and of uncertain scope. Defendants could therefore use "prodrug" to bootstrap the phosphoramidate prodrug moiety present in sofosbuvir within the scope of the R^9 and R^{10} groups. But as described above, the intrinsic record does not support such broad claim scope, and a skilled artisan would have been reasonably certain that it did not, despite the patent's use of the concept of a "prodrug" within the description of "administering."

Gilead's construction of "administering" should be adopted for these additional reasons, in the interest of preserving the claims' validity. *Rhine v. Casio, Inc.*, 183 F.3d 1342, 1345 (Fed. Cir. 1999) (providing that claims should be construed in a manner that would preserve the claim's validity).

V. CONCLUSION

For the foregoing reasons, as well as those to be stated at argument, Gilead respectfully requests that the Court adopt its proposed constructions.

Dated: November 17, 2014

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of the above and foregoing document has been served on November 17, 2014, to all counsel of record who are deemed to have consented to electronic service via the Court's CM/ECF system per Civil Local Rule 5-1(h)(1).

/s/ Douglas E. McCann
Douglas E. McCann